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Original article

Role of serum immunoglobulin E in patients with interstitial cystitis/bladder pain syndrome

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ABSTRACT

Objective: The actual pathophysiology of interstitial cystitis (IC)/bladder pain syndrome (BPS) is still uncertain. Immune or hypersensitivity mechanisms may play an important role in the pathogenesis of IC/BPS. This study was designed to investigate and analyze serum immunoglobulin E (IgE) levels in patients with IC/BPS.

Materials and methods: Patients with IC/BPS who were admitted for cystoscopic hydrodistention were enrolled in this study. Blood samples were obtained to investigate their serum IgE levels. A serum IgE level more than 200 IU/mL was considered abnormal. The patients' symptoms, visual analog scale (VAS) scores, O'Leary–Sant symptom (OSS) scores, cystometric bladder capacity (CBC), maximal bladder capacity (MBC), and grading of bladder glomerulation hemorrhage during cystoscopic hydrodistention were recorded. Serum IgE levels were also investigated in women with stress urinary incontinence, who served as the control group.

Results: Two hundred patients with IC/BPS and 35 controls were investigated. In total, 22 IC/BPS patients (11%) had abnormal serum IgE levels. No abnormal serum IgE levels were detected in the controls. The mean serum IgE level in IC/BPS patients and controls were 102.37 IU/mL ± 250.68 IU/mL and 74.21 IU/mL ± 88.62 IU/mL, respectively ($p = 0.204$). The VAS, OSS, CBC, MBC, and grading of glomerulations were not significantly correlated with serum IgE levels ($p = 0.317$, 0.587, 0.774, 0.559, and 0.309, respectively). The serum IgE levels were slightly higher in men than in women, although the difference was not significant (152.98 IU/mL ± 201.73 IU/mL vs. 94.87 IU/mL ± 262.54 IU/mL, $p = 0.183$).

Conclusion: In this study, 11% of patients with IC/BPS had IgE level more than 200 IU/mL, but the mean serum IgE level was not higher than the controls. Aggravating factors such as food or environmental substance should be carefully investigated in IC/BPS patients with elevated serum IgE levels.

1. Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a clinical syndrome characterized by bladder pain and urinary frequency.[1] The prevalence of IC/BPS ranges from 52 to 500/100,000 in women compared with 8–41/100,000 in men, and its incidence has increased globally in recent years.[2] Although many studies have investigated the pathophysiology of IC/BPS in the past 20 years, it remains a mystery. Many different hypotheses had been proposed, including infection, inflammation, autoimmune mechanisms, defects in the urothelial glycosaminoglycan layer, and central neurologic mechanisms.[3] The etiology or pathogenesis of IC/BPS might not be the same in every patient.

The histopathology of IC/BPS is not universal or specific. In a previous study, 55% patients with IC/BPS had a normal bladder histology, which was indistinguishable from that in controls.[4] However, some bladder specimens of patients with IC/BPS were characterized by mononuclear inflammation and mast cell activation.[4] Eosinophil infiltration has also been found in some patients with IC/BPS.[4] Liu et al[5] quantitatively evaluated the expression of junction protein E-cadherin, tight junction protein zonula occludens, and activated mast cells in the bladder wall using immunofluorescence staining and found significantly increased numbers of mast cells in biopsy specimens from patients with IC/BPS compared with those from normal controls.[5] The vasoactive amines, cytokines, and chemokines released by mast cells might play an important role in the pathogenesis of IC/

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BPS.[6] Mast cells could be activated through their Fc receptors by anaphylatoxins, neuropeptides, cytokines, and immunoglobulin E (IgE).[7]

Mast cells and IgE are essential components of allergic inflammation, and a previous study suggested that elevated serum IgE levels could be detected in some hypersensitivity diseases such as asthma and allergic rhinitis.[8] Yamada[9] performed cutaneous IgE radioallergosorbent tests (RASTs) to identify possible allergens in patients with IC/BPS, and carried out intravesical provocation tests with the IgE-RAST-positive antigens. The IgE-RAST-positive antigen was identified in four of five patients. In another study, approximately 80% of IC/BPS patients (children and adolescents) had complications of allergic diseases.[10] Jhang et al[11] also found increased serum IgE levels in patients with ketamine-related cystitis and in that study, the maximal bladder capacity (MBC) was correlated with the serum IgE level. IgE–mast cell-mediated inflammation in the bladder might participate in the pathogenesis of IC/BPS, and abnormal elevation of the serum IgE level might be detected. This study was designed to investigate the serum IgE level in patients with IC/BPS and its correlation with clinical symptoms.

2. Materials and methods

Patients with IC/BPS who were admitted to Hualien Tzu Chi General Hospital for treatment from 2008 to 2014 were enrolled in this study. Their comprehensive clinical symptoms, disease history, blood tests including a complete blood count and biochemistry study, urinalysis, and urodynamic study were investigated in our clinic. Patients who did not meet the National Institute of Diabetes and Digestive and Kidney Diseases criteria for IC/PBS were excluded before enrollment.[12] All patients underwent cystoscopic hydrodistention during hospitalization. The hydrodistention was performed under general or spinal anesthesia with direct vision by cystoscopy and irrigation fluid was instilled into the bladder at a pressure of 80 cmH_2O. The diagnosis of IC/PBS was confirmed by findings of glomerulation hemorrhage during cystoscopic hydrodistention. All of these patients had failed treatment with oral pentosan polysulfate, pain control drugs, and lifestyle modification. Patients who had allergic rhinitis, allergic dermatitis, allergic enterocolitis, drug allergies, or evidence of infection in any organ in the previous month were excluded. Patients with pyuria on urinalysis, a history of urinary tract surgery, malignant neoplasm, and severe systemic disease requiring hospitalization in the previous month were also excluded from this study. Serum IgE levels were also investigated in the control group, which consisted of patients with stress urinary incontinence without any allergic disease history.

Symptom severity was evaluated in patients using the O'Leary–Sant symptom (OSS) score and pain was evaluated using the visual *analog* scale (VAS) score. The cystometric bladder capacity (CBC) results in the urodynamic study were recorded. The study patients were classified into ulcer or nonulcer groups according to cystoscopic findings. The MBC and grading of glomerulation hemorrhage (graded from 0 to 4, indicating none, mild, moderate, severe, and ulcerated, respectively) during cystoscopic hydrodistention were also recorded.[13] Blood samples were collected during cystoscopic hydrodistention and serum IgE levels were determined. The serum IgE level was measured using a solid-phase immunoassay (Phadia specific immunoglobulin FEIA, Uppsala, Sweden), and a serum IgE level more than 200 IU/mL was considered abnormal.[14] If the patients agreed, bladder mucosal tissues measuring about 2×2 mm^2 were obtained during cystoscopic hydrodistention.

The bladder tissues were investigated for mast cell activation by measuring the tryptase level. Biopsy specimens were embedded in optimal cutting temperature media and stored at −80°C. The sections were incubated overnight at 4°C with primary antibodies to antihuman tryptase (Chemicon, Temecula, CA, USA). Immunofluorescence tryptase assays were quantified by counting the number of positively stained cells/total cells/unit area (4 μm^2), and shown as the percentage of positive cells/100 total cells. Patients were subsequently treated with intravesical onabotulinum toxin (Botox) injections or intravesical hyaluronic acid (Cystistat) installation. The treatment outcomes were assessed using the Global Response Assessment (GRA) tool 3 months after initial treatment. Patients were requested to rate their bladder symptoms compared with baseline on a 7-point centered scale [markedly (−3), moderately (−2), slightly worse (−1), no change (0), slightly (+1), moderately (+2), or markedly improved (+3)].[15]

The baseline OSS, VAS, CBC, and MBC values were compared between IC/BPS patients with normal and abnormal serum IgE levels using the independent *t* test. The correlations of these parameters with serum IgE were investigated. The GRA scores were also compared between patients with normal and abnormal serum IgE levels. The correlation between expressions of tryptase and serum IgE was also investigated. Statistical assessments were considered significant when p is less than 0.05. Statistical analysis was performed using SPSS version 15 (SPSS Inc, Chicago, IL, USA). This study was approved by the Institutional Review Board and Ethics Committee of Hualien Tzu Chi hospital. Each patient was informed about the study rationale and procedures before enrollment in the study; written, informed consent was obtained before treatment.

3. Results

A total of 200 patients including 38 men and 162 women were recruited to this study and completed initial investigations. The mean age of these patients was 49.36 years ± 13.54 years (mean age of male patients, 48.52 years ± 12.77 years; mean age of female patients, 49.55 years). The serum IgE level was investigated in 35 female controls (mean age 53.4 years ± 12.12 years). There was no significant difference in age between IC/BPS patients and controls. The mean serum IgE level of the IC/BPS patients was 102.37 IU/mL ± 250.68 IU/mL, and the median serum IgE level was 39.5 IU/mL. The mean serum IgE level in the control group was 74.21 IU/mL ± 88.62 IU/mL. There was no statistically significant difference in the serum IgE level between IC/BPS patients and the controls ($p = 0.204$). After excluding male patients in the IC/BPS group, the difference between IC/BPS patients and controls was still not significant ($p = 0.215$). Twenty-two (11%) of the 200 IC/BPS patients had abnormal serum IgE levels. Three patients with abnormal IgE levels, and 19 patients with normal serum IgE levels had a history of allergy to drugs or food ($p = 0.732$). None of the individuals in the control group had an abnormal serum IgE level.

The mean serum IgE levels in male and female IC/BPS patients were not significantly different statistically (124.16 IU/mL ± 160.66 IU/mL vs. 97.17 IU/mL ± 267.90 IU/mL, respectively, $p = 0.552$). Twelve patients had ulcer-type IC/BPS. There was no significant difference in the mean serum IgE level between patients with the ulcer and nonulcer types of IC/BPS (225.69 IU/mL ± 590.36 IU/mL vs. 94.38 IU/mL ± 212.28 IU/mL, respectively, $p = 0.459$). The age, VAS, OSS, CBC, MBC, and grading of glomerulation hemorrhage after cystoscopic hydrodistention between patients with normal and abnormal serum IgE levels were not significantly different (all $p > 0.05$; Table 1). The age, VAS, OSS, CBC, MBC, and grading of glomerulation also did not significantly correlate with serum IgE levels ($p = 0.157$, 0.317, 0.587, 0.774, 0.559, and 0.309, respectively). A total of 19 patients agreed to bladder biopsies, and investigation of their tryptase level. The correlation between the IgE level and expression of tryptase was not significant ($p = 0.958$, $r^2 = 0.001$).

Table 1
Baseline parameters in patients with normal and abnormal serum IgE levels.

	Abnormal IgE ($N = 22$)	Normal IgE ($N = 178$)	p
Age (y)	54.59 ± 17.88	48.67 ± 12.78	0.146
CBC (mL)	271.73 ± 96.10	300.55 ± 118.49	0.369
OSS score	24.47 ± 5.78	24.74 ± 6.87	0.897
VAS score	5.73 ± 2.67	4.59 ± 2.57	0.108
MBC (mL)	635.29 ± 181.80	674.68 ± 180.36	0.402
Glomerulation hemorrhage grading	1.76 ± 1.09	1.75 ± 1.02	0.946

CBC = cystometric bladder capacity; IgE = immunoglobulin E; MBC = maximal bladder capacity; OSS score = O'Leary–Sant symptom score; VAS = visual analog scale.

A total of 100 patients received intravesical onabotulinum toxin injections and 31 patients received intravesical hyaluronic acid installation. Among the patients who received onabotulinum toxin injections, the mean GRA score was 1.70 ± 0.67 in those with abnormal IgE ($n = 10$) levels and 1.44 ± 0.86 in those with normal IgE ($n = 90$) levels, with no significant difference ($p = 0.291$). Among the patients who received intravesical hyaluronic acid installation, the mean GRA score was 1.33 ± 0.58 in those with abnormal IgE levels ($n = 3$) and 1.36 ± 0.83 in those with normal serum IgE ($n = 28$) levels; however, there was no significant difference ($p = 0.962$).

4. Discussion

Previous studies have suggested that IC/PBS has a multifactorial etiology that may act predominantly through one or more pathways resulting in the typical symptom complex.[16] It is possible that no single treatment is effective for all IC/BPS patients. One case report revealed causative participation of inhalant allergens and food components in urinary complaints.[17] Elimination of food products that resulted in the production of specific IgE antibodies and positive skin reactions resulted in a favorable clinical response in some IC/BPS patients.[18] Hypersensitivity and bladder IgE have also been reported to be associated with IC/BPS.[8,11] In this study, approximately 11% of IC/BPS patients had abnormal elevated serum IgE level, whereas none of the individuals in the control group had any abnormal serum IgE level. However, the mean serum IgE level was not different between the two groups.

A report 20 years ago noted that acidic food, alcohol, coffee, and tea increased IC pain in some IC/BPS patients.[19] Friedlander et al[20] also reported that up to 90% of patients with IC/BPS had sensitivities to a wide variety of comestibles. One commonly held theory proposes that the dysregulated bladder urothelial barrier leads to the migration of urinary solutes or cations across the urothelium with subsequent provocation of IC/BPS symptoms.[21,22] However, these studies were small and underpowered investigations carried out on few patients.[20] In theory, cations passing through the urothelium should not induce an inflammatory reaction in healthy tissue. Hypersensitivity, which is characterized by a reaction immediately following contact with innocuous antigens, is compatible with the clinical history of IC/BPS, and is another possible mechanism. According to histopathologic findings of increasing mast cell infiltration in the suburothelium and elevated serum IgE levels in some patients, we suggest that the IC/BPS in some patients who are sensitive to foods might result from an IgE–mast cell-mediated inflammation response.

European Urology Association guidelines suggest that IC/BPS patients should be classified by the findings of cystoscopic hydrodistention and bladder biopsy.[1] Leiby et al[23] also reported that the histopathological features in biopsy specimens from IC/BPS patients were significantly correlated with the severity of symptoms. Mast cell infiltration in the suburothelium in IC/BPS cases has been well reported in many studies, and the increasing expression of mast cells could also be correlated with symptoms.[4,5] Mast cell-mediated inflammation plays an important role in inflammation in IC/BPS patients. Mast cells are stimulated by cross-linking of IgE bound to surface receptors (FcεRI) and by specific antigens.[24] Mast cell activation, development, and migration are mediated by IgE.[24] Mast cells and IgE have been so convincingly linked to the pathophysiology of allergic reactions that it can be difficult to think of them in other contexts.[25] However, serum IgE is not a good biomarker for a hypersensitivity disease. In one study, the mean serum IgE was not elevated and had poor correlation with clinical symptoms, even in allergic rhinitis.[26] In this study, the mean serum IgE level in IC/BPS was not significantly higher than that in the normal controls (102.37 IU/mL ± 250.68 IU/mL vs. 74.21 IU/mL ± 88.62 IU/mL, $p = 0.204$), and serum IgE levels were also not correlated with symptoms. The mast cell activity in immunochemical staining and serum IgE also did not have a significant correlation. The half-life of IgE could be weeks to months if it is bound to cells in tissue, but would be only about 6 hours when IgE is free in the plasma.[27] IgE–mast cell-mediated inflammation might participate in the pathogenesis in some IC/BPS cases, but the short half-life of serum IgE might lead to a poor correlation with clinical symptoms.

Our study is a preliminary investigation about the possible relation of IgE and IC/BPS. It implies the pathogenic association between IC/BPS and hypersensitivity, at least in some of these patients. Because some patients had abnormal elevation of serum IgE levels, we suggest that physicians should investigate for any aggravating factors of IC/BPS symptoms in these patients (such as food or environmental substance). The main limitation of this study was the lack of a well-accepted definition of normal serum IgE in middle-aged adults, and therefore, the definition of abnormal serum IgE might be inappropriate. The control group only included women, but the study group included 19% male patients. We could not eliminate the sex difference and prostate influence between the two groups. The mean serum IgE might decrease with age and female sex.[28] In the control group, some patients with stress urinary incontinence may also have urgency/frequency or other urologic conditions, and this might affect the serum IgE level. These data might be heavily weighted by some extreme values. Further immunohistochemical studies investigating local deposition of IgE in bladder specimens, *in vitro* stimulation tests, and patch tests of a large IC/BPS cohort might be helpful in this regard. The correlation between serum IgE and mast cell infiltration in the suburothelium should also be investigated.

5. Conclusion

Elevated serum IgE level (>200 IU/mL) was found in 11% patients with IC/BPS. However, the mean serum IgE levels in these

patients were not higher than those in the controls. While examining IC/BPS patients with elevated serum IgE levels, physicians should be careful if their patients are allergic to any substance that could induce or aggravate the symptoms.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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